REMARKS

In view of the following remarks, the Examiner is respectfully requested to allow Claims 1-18 and 24-28, the only claims pending and currently under examination in this application.

The Examiner is thanked for the personal interview held with the undersigned and Dr. Bradley Galer on March 25, 2008. During the interview, the rejection of the claims as obvious over Freidman in view of Oda were discussed. The undersigned and Dr. Galer highlighted for the Examiner how the combined teaching of the references did not teach or suggest the elements of the pending claims and that the record has substantial factual evidence in the form of several 1.132 declarations of record which demonstrate how one could not have predicted success of the claimed invention prior to the work reported in the application. The Examiner indicated that the positions put forth by the undersigned and Dr. Galer appeared convincing, and requested that when a formal written response to the Final Rejection was made, that such a response include a discussion of the hypothesized mechanism of action by which the claimed invention is believed to work. It is believed that the above discuss provides a true summary of the points discussed during the personal interview.

In the above amendments, Claims 19 – 23 have been cancelled without prejudice. As the amendments introduce no new matter, their entry by the Examiner is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Claims 1-28 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Freidman (U.S. Patent No. 6,139,861) in view of Oda et al. (U.S. Patent No. 5,725,874).

In making this rejection, the Examiner asserts that combined teaching of the two cited references renders the claimed invention obvious. Specifically, the

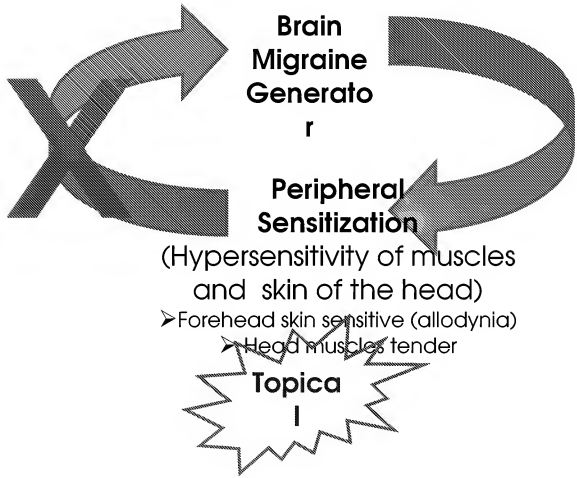
Examiner states that Freidman teaches treatment of migraine or tension headaches by topical administration of NSAID and that Oda teaches administration to the skin.

The claims are directed to methods of ameliorating headache pain. Headache pain that is ameliorated by the practicing the methods is the pain that is perceived to be in the brain, and is pain that originates in the central nervous system. An element of all of the claims at issue is: "topically applying an effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in said topical formulation to a keratinized skin surface of the head of said host... **wherein said topically applied NSAID only acts locally.**" As such, the claims are limited to methods where the formulation is only applied to a keratinized skin surface of a head of host, and only to a region of the head where the NSAID acts only locally at the site of application at the keratinized skin surface of the head, as opposed to systemically or locally anywhere else in the body. As developed below, this element of the claims is neither taught nor suggested in the cited combination of references.

The claimed invention is based on the surprising and unexpected discovery that applying a topical NSAID to the keratinized skin of the head that does not produce any meaningful systemic blood levels (i.e., orders of magnitude below that produced by administering a therapeutic oral or rectal or intravenous dose of the same medication) results in alleviation of headache pain, i.e., pain perceived to be in the brain. The inventors of the present application found that, contrary to accepted belief of those of ordinary skill in the art at the time the application was filed, one could treat the migraine headache and reduce the pain of the headache felt in the brain by applying a topical NSAID formulation to a keratinized skin surface of the head, e.g., the forehead, in a manner such that the NSAID acts only locally.

It is hypothesized that the mechanism of action of topically applying an NSAID to the keratinized skin surface of the head ameliorates headache pain via a direct anti-

inflammatory effect on tender and sensitized muscles and peripheral nerves directly underlying the keratinized skin of the head where the topical NSAID is applied. This local action results in closing a feedback loop of peripheral nociception into the brain, where central headaches originate. In other words, a vicious cycle is broken by stopping the nerve signals being caused by tender and sensitive muscles and skin in the head, usually in the forehead and occiput regions, as illustrated in the figure below.

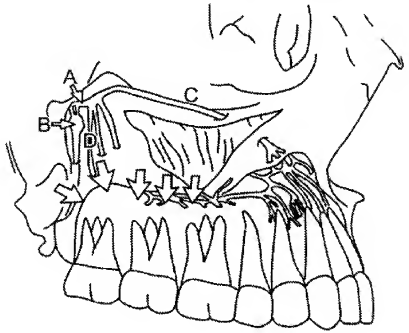


In contrast to this element of the present claims, Friedman teaches a distinctly different specific placement for an NSAID drug: "…topically applying **directly to the mucous membrane of the mouth in the maxillary third molar apical area**…." See

Figure 2 of Friedman, reproduced below:

Fig. 2

Maxillary Nerve Plexus (arrows)



Thus, Friedman's proposed mechanism of action is distinct from that of the current invention. As stated in the Friedman patent (column 3, lines 30-33): "The object of this invention is to reduce or eliminate this intraoral inflammation localized in the maxillary third molar apical area." Furthermore, the examples described by Friedman use intraoral chilling (not NSAID) (Column 2, lines 11 – 44) where he states there is a "local vasoconstrictor effect" (line 42). There is no mention or description or claim of applying NSAID medication topically to anywhere else in the body, solely and specifically this invention only describes application at this intraoral "periapical areas of the posterior molar teeth" since his invention's basis is that headache patients have a "distinct area of maxillary alveolar tenderness" with a "localized inflammation" that is

responsible for their headache. Therefore, the underlying tenet and hypothesized mechanism of intraoral chilling or application of an NSAID of Freidman in no manner describes, teaches or infers the current discovery and invention.

One way scientists and clinicians test for the function of a nerve is to block its activity or "numb" it, usually by injection of a local anesthetic drug, such as lidocaine (Novacaine). When one injects lidocaine into the area described by Friedman, the person will experience a loss of sensation (numbness) in the molar teeth, sinuses, and areas of the mouth that are supplied by the nerve that has been numbed. There is no loss of sensation in the head keratinized skin of the forehead and occiput regions. For example if the dentist was working on a tooth at the bottom of the left side of your mouth, he would inject the anesthetic agent around that tooth. If he were to inject on the other side of your mouth instead, the area being worked on would not be numbed.

In contrast, when one injects a local anesthetic, such as lidocaine, into the muscles and tissues underlying the keratinized skin surface of the head (the target site of topical NSAID application specified in the pending claims of the present application), the person will experience a loss of sensation (numbness) only in the skin and muscle areas of the head where the lidocaine was injected- there is no loss of sensation in the molar teeth, sinuses, and areas of the mouth. (That is why a dentist will inject a local anesthetic directly into the mouth/gums area prior to a painful procedure and not inject the local anesthetic into the keratinized skin of one's forehead.and/or occiput.)

Furthermore, topically applying a NSAID to the "periapical areas of the posterior molar teeth" as claimed by Friedman would have no effect on the pathophysiologic changes that are occurring in the headache patient's forehead or occipital tender keratinized skin and muscle regions of the head and conversely, applying a topical NSAID to the keratinized skin of the head would not affect Friedman's hypothesized "intraoral inflammation localized in the maxillary third molar apical area" in headache patients. The two inventions, hypothesized mechanisms of action, and treatments are

completely distinct .

Thus as described above, when treating a medical condition, such as headache, with a topical drug, meaning only consisting of a local effect (not systemic), the specific placement of the topical drug on the body is critical to the success of that treatment. Since the topical drug can only exert its activity on tissues in which it directly interacts, application of an NSAID directly to the mucous membrane of the mouth in the maxillary third molar apical area will not have the same effect as applying an NSAID to a keratinized skin surface of the head.

Moreover, it is not obvious to those knowledgeable in the art of treating headache conditions that successful treatment by placing an NSAID "directly to the mucous membrane of the mouth in the maxillary third molar apical area" would suggest that topically applying an NSAID to the "keratinized skin surface of the head" would also result in amelioration of headache symptoms. These areas are composed of very different tissues and nerves. Furthermore, at the time of this invention, headache authorities did not nor would not have conceived of treatment with application of an NSAID topically to the keratinized skin surface of the head whereby the NSAID acted only locally because (1) authorities in the field believed the underlying biologic pathophysiologic mechanism of migraine, indomethacin responsive headache, central tension type headache and other headache conditions was related to abnormalities solely within the brain and (2) NSAIDs would only successfully treat headache symptoms if large clinically meaningful blood levels were achieved, i.e., topically delivered drugs result in systemic drug levels orders of magnitude less than those achieved by by intravenous, oral or rectally delivered dosing.

Freidman solely teaches applying a drug including an NSAID onto **the mucous membrane of the mouth** in order to treat headache pain. Friedman teaches an exact location for placement of his drug because he believes there is an inflammatory focus in the "plexus formed by the posterior superior alveolar

branch of the ipsilateral maxillary nerve" whereby only intraoral placement "in the maxillary third molar apical area" would produce his clinical results.

As the Applicants presented in the previous response filed October 5, 2007, Freidman's formulation is likely to also result in **systemic delivery**[1] of the active agent.

Oda teaches applying a solubilizer and a drug to the skin. The solubilizer improves and enhances delivery of active medication into **systemic circulation**, since the vast majority of the drug classes listed in Oda only have a clinically meaningful effect if they enter the circulation in clinically significant amounts, such as central nervous stimulants, hormones, antihypertensive agents, cardiotonics, antiarrhythmic agents, coronary vasodilators, antineoplastic agents, antiepileptics, anti-Parkinson agents, assistant to the prohibition of smoking, and vitamins. Oda, Col. 2, line 52 to Col. 3, line 27. As such, Oda does not teach that the drug would work only locally.

Furthermore, Oda does not teach application to the skin of the head area. Instead, Test Examples 4 and 6 of Oda teach applications of an agent of interest to the **upper back** of a subject.

> In order to test human percutaneous absorption, the samples of Example 4 and Comparative Example 2 in Test Example 4, or the samples of Example 9 and Comparative Example 6 in Test Example 6 were applied to the **upper backs** of eight healthy subjects respectively.

[1] "As Friedman himself writes 'The rate of absorption through the mucous membrane is rapid.' Applying drugs, even in a small surface area, to the oral mucous membranes results in rapid delivery of drug to the systemic circulation due to the highly vascular nature of the intraoral mucosal tissues. As stated in an industry report '...the permeability of mucous membranes provides a convenient route for the systemic delivery of new and existing therapeutic drugs. Transmucosal delivery offers the potential for once daily dosing of oral drugs and avoids the effects of first pass metabolism.' [www.medicalnewstoday.com/articles/65620.php] A report from the University of Alberta that was published in J Pharm Pharmaceut Sci 1 (1):15-30, 1998 states: 'Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable.' Furthermore, this report outlines the cellular structure and characteristics of the oral mucosa, which are dramatically distinct from that of keratinized skin. [http://www.ualberta.ca/~csps/JPPS1(1)/A.Shojaei/buccalreview.htm]" Applicants' previous response filed October 5, 2007, page 11, last paragraph – page 12, first paragraph.

Oda, column 32, lines 46-49; column 33, lines 41-44.

Therefore, Freidman discloses administration of an NSAID through the mucous membrane of the mouth and Oda discloses topical formulations for application to the back. As described above, both Freidman's and Oda's formulations are likely to result in systemic delivery of the active agent, such that one of ordinary skill in the art would view Freidman and Oda as directed to systemic delivery of an active agent. Therefore, one of ordinary skill in the art would view Freidman and Oda as teaching and suggesting application of a topical formulation to a location that would provide for systemic delivery, as opposed to local delivery.

As such, neither Freidman nor Oda teaches or suggests topical application of an NSAID to a keratinized skin surface of a head, and specifically to a location where the NSAID acts only locally, as claimed.

In attempting to rebut this position, the Examiner states that the formulation including the drug controls the delivery of the drug and that, since the Applicants do not disclose any formulation, the cited prior art reads on the claims. The Applicants respectfully disagree with the Examiner and submit that the **location of application** also plays a critical role on whether a drug is delivered systemically or locally.

There has been research evidencing that application of the same drug to different anatomical sites of the body may result in different deliveries of the drug. In particular, application of a drug to the back is more likely to result in systemic circulation. For example, an NSAID topically applied to 1) back, 2) arm, and 3) knee showed higher plasma ketoprofen C(max) when applied to the back and arm than to the knee. Shah AK at abstract[2]. Also, parathion applied to 1)

[2] Ketoprofen, an NSAID, was applied topically to different anatomical sites on the body of 24 healthy

abdomen, 2) buttocks, 3) back and 4) shoulder exhibited the highest absorption when applied to the back. Qiao, Abstract[3]. Therefore, absorption of a drug is different depending on the anatomical sites of the body to which the drug is applied. As such, location of application also has an impact on the whether a drug is delivered systemically or locally. Accordingly, the Examiner's reliance solely on the formulation is misguided.

Furthermore, the Applicants contend that Freidman in view of Oda, fails to provide one of skill in the art with predicted success in the claimed invention. As mentioned earlier, the results of this invention were unexpected and surprising based on knowledge and the state of the prior art among the headache scientific and clinical community. The Examiner is reminded that inventors Dr. Bradley Galer and Dr. Lawrence Newman are considered experts in the field.

MPEP § 2145 sets out the principles in considering rebuttal arguments by applicants against obviousness, stating in part that: "Rebuttal evidence may also include evidence that the claimed invention yields **unexpectedly improved properties or properties not present in the prior art**. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties." (emphasis added)

The "predicted success" of a combination of elements is an important factor in determining obviousness. This principle is illustrated in *three* Supreme

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subjects – 1) back, 2) arm, and 3) knee. Pharm Res. 1996 Jan; 13(1):168-72, abstract. Plasma samples were obtained for the assay of racemic ketoprofen and ketoprofen enantiomers. Id. The plasma ketoprofen C(max) applied to the back and arm were similar ($p > 0.05$) but C(max) was lower when applied to the knee was ($p < 0.05$) lower. Id.

[3] 2,6-[ring-14C]parathion was applied to four different anatomical sites on the body in weanling swine using occluded and nonoccluded dosing systems – 1) abdomen, 2) buttocks, 3) back and 3) shoulder. Qiao GL, Toxicol Appl Pharmacol. 1993 Sep;122(1):131-8, Abstract. Total urinary and fecal excretion (%dose) by 168 hr were, for the occluded system, 43.94 +/- 2.24 (abdomen), 48.47 +/- 7.85 (buttocks), 48.82 +/- 4.49 (back), and 29.28 +/- 5.70% (abdomen), and for the nonoccluded system, 7.47 +/- 2.16 (abdomen), 15.60 +/- 3.71 (buttocks), 25.00 +/- 8.75 (back), and 17.41 +/- 1.76% (abdomen). Id. Therefore, for both the occluded and nonoccluded systems, the absorptions from the back were the highest. Id.

Court cases[4] decided prior to *KSR*, and is a recurring theme of *KSR*. For example, in *KSR* the Supreme Court stated that in order for a combination of elements to be patentable "the combination must do more than yield a predictable result". [5] Likewise, the corollary principle, namely that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"[6] is also discussed. The Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions".[7]

Thus, according to the Supreme Court, an analysis of the "predictable success" of a combination of known elements may be used to separate patentable combinations (e.g., a battery that contains water, in the case of *United States* v. *Adams*, *supra*) from those that are unpatentable (e.g., an adjustable pedal having a fixed pivot point and a sensor, in the case of *KSR, supra*).

Neither Freidman nor Oda teaches that an NSAID could be applied to the keratinized skin of head area or that a topically applied NSAID could be effective while it acts locally, as opposed to systemic administration of the NSAID. At best, both of the cited references suggest use of an NSAID formulation through its systemic delivery to the subject. Directly contrary to the suggestions by Freidman or Oda, the Applicants found that an NSAID formulation upon applying to the skin of the head area treats a headache by acting only locally.

Furthermore, prior to the Applicants' work reported in the Specification, the common belief in the relevant art was that a topical formulation of NSAID that is effective by acting only locally would not be able to supply a therapeutically

[4] *United States* v. *Adams*, 383 U.S. 39, 40 (1966); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.C. 57, 60-62 (1969) and *Sakraida* v. *AG Pro, Inc.*, 425 U.C. 273, 282 (1976).
[5] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).
[6] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007).
[7] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007); emphasis added.

effective level of NSAID to treat the claimed headache via systemic activity. The Declaration by Lawrence C. Newman, M.D., filed for the parent application on December 10, 2002, evidences this belief for indomethacin, an NSAID. The Declaration is enclosed herewith.

> Prior to my work in this area as embodied in the present application and claims, it was my expectation, which is the same as with what those of skill in the art would expect, that a topical formulation of indomethacin would not be able to supply **therapeutically effective levels of indomethacin** to be able to successfully treat indomethacin-responsive headaches. As such, prior to my work in this area, the methods of treating indomethacin-responsive headaches involved only oral and rectal administration of indomethacin, because it was believed that only oral and rectal formulations (not topical formulations) could supply sufficient levels of indomethacin to treat indomethacin-responsive headaches. Thus at that time, there was an extremely low expectation of success that a topical formulation of indomethacin could supply a therapeutically effective amount of indomethacin to successfully treat indomethacin-responsive headaches.
>
> The present application and claims are based on our discovery of the unexpected result that a topical formulation of indomethacin provides a therapeutically effective method of treating indomethacin-responsive headaches.
>
> Declaration by Lawrence C. Newman, M.D. filed for the parent application on December 10, 2002,

As such, one of ordinary skill in the art, even in view of Freidman and Oda, would not reasonably expect that an NSAID formulation topically applied to the head area in a manner that it acts only locally could treat headache with predictable success under the *KSR* standard.

In light of the above arguments, it is submitted that: 1) the combined teaching of Freidman in view of Oda fails to teach or suggest all of the elements of the claimed methods; and 2) the cited combination of references fails to provide the requisite predicted success in the claimed invention. Accordingly,

Claims 1 to 28 are not obvious under 35 U.S.C. § 103(a) over Freidman (U.S. Patent No. 6,139,861) in view of Oda et al. (U.S. Patent No. 5,725,874) and this rejection may be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, reference no. TOPI-002CIP.

Respectfully submitted,

Date: March 31, 2008

By: /Bret E. Field, Reg. No. 37,620/
Bret E. Field
Registration No. 37,620

Enc.

- Declaration by Lawrence C. Newman, M.D. filed for the parent application 09/755,592 on December 10, 2002,

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